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PATENT SPECIFICATION

NO DRAWINGS

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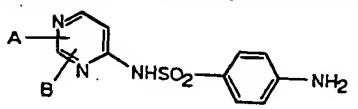
COMPLETE SPECIFICATION

Novel 4-Sulfanilamido-Pyrimidines and their Salts and processes for the manufacture thereof

We, CHUGAI SEIYAKU KABUSHIKI KAISHA, a joint stock company organised under the laws of Japan, of No. 3, Nihonbashi Honcho 3-Chome, Chuo-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

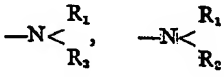
The present invention relates to novel 4-sulfanilamido-pyrimidines having a substituted amino radical in the pyrimidine nucleus represented by the following general formula:



- - - - (I)

wherein A and B are respectively atoms or radicals at the 2 position and 6 position, one of them represents always

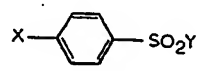
and the other hydrogen, halogen, alkoxy, alkylthio or



being a radical in which R_1 and R_2 are aliphatic hydrocarbon residues or which forms a heterocyclic ring which may contain an oxygen or sulfur atom in addition to R_1, R_2 and the adjacent nitrogen atom, and their salts.

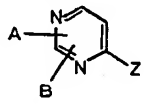
The present invention relates also to the processes for manufacturing novel 4-sulfanilamido-pyrimidines having a substituted amino radical in the pyrimidine nucleus represented by the aforementioned general formula (I) and their salts.

According to the present invention there is provided a process which comprises condensing the compounds represented by the general formula:



- - - - (II)

wherein X is an amino radical or nitro, acylamino, alkoxycarbonylamino or azo radical and Y is NH_2, NHNa or halogen, with compounds represented by the general formula:



- - - - (III)

wherein A and B are the same groups as above and Z is NH_2, NHNa, halogen or $N(CH_3)_3Cl$, but one of Y and Z is NH_2 or NHNa and the other is a halogen or $XN(CH_3)_3Cl$, and if necessary converting the substituted X into an amino radical.

In the case in which a compound (II) in which Y is halogen, especially chlorine is used, that is to say, when a benzenesulfonylchloride having at the *p*-position a substituent capable of being converted into an amino radical by hydrolysis or reduction is caused to react with a compound in which Z is an amino radical,

[*Price 4s. 6d.*]

that is to say a 4-amino-pyrimidine derivative, it is preferable to use a solvent, for example pyridine, and to perform the reaction at room temperature. Then the reaction product is subjected to hydrolysis or reduction to convert the substituent at the *p*-position into an amino radical, whereupon the desired compound (I) may be obtained. If the hydrolysis is performed with caustic potash or caustic soda, the dissolution of the reaction product is so difficult that the decomposition reaction does not proceed smoothly, owing to the influence of the substituted amino radical in the pyrimidine nucleus. In this case, the reaction may be accelerated by addition of a lower alcohol such as, for example, methanol, ethanol and the like.

A compound (II) in which Y is an amino radical may be reacted with a compound (III) in which Z is, for example, a halogen or a trimethyl ammonium chloride group by known procedure. In this case, if the reaction product having a sulfanilamido group

$$(—SO_2—NH—)$$

formed has as X a substituent capable of being converted into an amino radical, the transformation of the X into an amino radical may be carried out by hydrolysis or reduction.

The novel 4-sulfanilamido-pyrimidine derivatives of the present invention may be caused to react, by known procedure, with alkaline substances, e.g. alkali-metal carbonates, alkali-metal hydroxides or organic bases to give their salts.

The novel products of the present invention are useful particularly in the therapy of bacterial infection as so-called sulfa drugs.

The present invention will be illustrated by way of example in the following examples.

Example 1.
2-methoxy-6-dimethylamino-4-sulfanilamido-pyrimidine

1.68 g. (0.01 mol) of 2 - methoxy - 6-dimethylamino - 4 - amino - pyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzene-sulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and the solution kept to stand for one night at room temperature. Thereafter 100 c.c. of water were added to the solution and then the product deposited was separated and dried. It was dissolved in methanol under heating and treated with activated carbon. On the concentration of the solution to one third of its volume and leaving to stand, while needle crystals of 2 - methoxy-6 - dimethylamino - 4 - acetylsulfanilamido-pyrimidine were obtained. Said crystals were recrystallized from methanol. m.p. 218—220°C,. Yield 3.4 g.

Elemental analysis $C_{15}H_{19}O_4N_5S$):

Calc.	C: 49.31%,	H: 5.24%,	N: 19.19%
Found	C: 49.56%,	H: 5.46%,	N: 19.00%

A solution of 3.4 g. of the 2 - methoxy-6 - dimethylamino - 4 - acetylsulfanilamido-pyrimidine thus obtained, in 30 c.c. of a 10% aqueous solution of sodium hydroxide was heated at 90°C. for one hour. After cooling, acetic acid was added to the solution to deposit an oily substance which crystallized on standing. After filtration it was recrystallized from dilute methanol to give white scaly crystals of the desired product. m.p. 207°C., yield 2.9 g.

Elemental analysis ($C_{13}H_{17}O_3N_5S$):

Calc.	C: 48.29%,	H: 5.30%,	N: 2.166%
Found	C: 48.02%,	H: 5.42%,	N: 21.51%

Example 2.
2-ethoxy-6-dimethylamino-4-sulfanilamido-pyrimidine

1.82 g. (0.01 mol) of 2 - ethoxy - 6-dimethylamino - 4 - aminopyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzene-sulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and then subjected to the same reaction procedure as in example 1. Recrystallization from methanol gave white needle crystals of 2 - ethoxy - 6 - dimethylamino - 4 - acetylsulfanilamido - pyrimidine. m.p. 230—234°C., yield 3.5 g.

Elemental analysis ($C_{16}H_{21}O_4N_5S$):

Calc.	C: 50.65%,	H: 5.58%,	N: 18.46%
Found	C: 50.54%,	H: 5.56%,	N: 18.70%

3.5 g. of 2 - ethoxy - 6 - dimethylamino-4 - acetylsulfanilamido - pyrimidine thus obtained were subjected to hydrolysis as in example 1. Recrystallization from dilute methanol gave white scaly crystals of the desired product. m.p. 228—230°C., yield 2.9 g.

Elemental analysis $C_{14}H_{19}O_3N_5S$):

Calc. C: 49.84%, H: 5.68%, N: 20.76%
Found C: 49.58%, H: 5.68%, N: 20.64%

EXAMPLE 3.
2-n-propoxy-6-dimethylamino-4-sulfanilamido-pyrimidine

1.96 g. (0.01 mol) of 2-n-propoxy-6-dimethyl - amino - 4 - amino - pyrimidine and 2.34 g. of *p*-acetamidobenzenesulfanylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from methanol gave light yellow columns of 2 - n - propoxy - 6 - dimethylamino - 4 - acetylsulfanilamido - pyrimidine. m.p. 215—216°C., yield 3.7 g.

Elemental analysis ($C_{17}H_{23}O_4N_5S$):

Calc. C: 51.90%, H: 5.89%, N: 17.80%
Found C: 51.90%, H: 5.80%, N: 17.54%

3.7 g. of 2 - n propoxy - 6 - dimethylamino - 4 - acetylsulfanilamido - pyrimidine thus obtained were subjected to hydrolysis as in example 1. Recrystallization from dilute methanol gave the desired white columns. m.p. 182—183°C., yield 3.1 g.

Elemental analysis ($C_{15}H_{21}O_3N_5S$):

Calc. C: 51.27%, H: 6.02%, N: 19.93%
Found C: 51.40%, H: 6.11%, N: 19.96%

EXAMPLE 4.
2-i-propoxy-6-dimethylamino-4-sulfanilamido-pyrimidine

1.96 g. (0.01 mol) of 2 - i - propoxy - 6-dimethylamino - 4 - amino - pyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzenesulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from methanol gave 2 - i - propoxy-6 - dimethylamino - 4 - acetylsulfanilamido-pyrimidine. m.p. 186—188°C., yield 3.7 g.

Elemental analysis ($C_{17}H_{23}O_4N_5S$):

Calc. C: 51.90%, H: 5.89%, N: 17.80%
Found C: 51.82%, H: 5.60%, N: 18.05%

3.7 g. of 2 - i - propoxy - 6 - dimethylamino - 4 - acetylsulfanilamido - pyrimidine thus obtained were dissolved in a mixture of 10 c.c. of concentrated hydrochloric acid and 100 c.c. of methanol and caused to react at 100°C. for 5 hours. After completion of the reaction, the reaction product was adjusted to pH 6.0 to give a deposit. Recrystallization from dilute methanol gave white scaly crystals of the desired product. m.p. 125—130°C., yield 3.2 g.

Elemental analysis ($C_{15}H_{21}O_3N_5S$):

Calc. C: 51.27%, H: 6.02%, N: 19.93%
Found C: 51.00%, H: 5.92%, N: 19.98%

EXAMPLE 5.
6-dimethylamino-4-sulfanilamido-pyrimidine

1.57 g. (0.01 mol) of 6 - dimethylamino-4 - chloropyrimidine, 3.44 g. (0.01 mol) of sulfanilamide, 2.76 g. (0.01 mol) of potassium carbonate and 0.75 g. (0.0126 mol) of sodium chloride were mixed well and heated with stirring on an oil bath. At a bath temperature of 135—140°C. and an internal temperature of 120°C. a violent reaction with bubbling was observed and the internal temperature rose to 150°C. The reaction was stopped in 4 minutes. The reaction product was dissolved in hot water and left to stand. The solids deposited were recovered by filtration and dissolved again in water. The solution was neutralized with 50% acetic acid. The precipitates thus formed were recovered by filtration and washed with water. Recrystallization from dilute methanol gave white scaly crystals of 6 - dimethylamino - 4 - sulfanilamido-pyrimidine. m.p. 276°C., yield 1.9 g.

Elemental analysis ($C_{12}H_{15}O_2N_5S$):

Calc.	C: 49.14%,	H: 5.16%,	N: 23.88%
Found	C: 49.04%,	H: 5.28%,	N: 23.88%

EXAMPLE 6.
2-dimethylamino-4-sulfanilamido-pyrimidine

1.38 g. (0.01 mol) of 2 - dimethylamino-4 - amino - pyrimidine and 2.2 g. (0.01 mol) of *p* - nitro - benzenesulfonylchloride were dissolved in 2.2 c.c. of anhydrous pyridine and left to stand at room temperature for one night. The reaction mixture was poured into 100 c.c. of water. Recrystallization of the deposit formed from dilute methanol gave 2 - dimethylamino - 4 - *p* - nitrobenzene-sulfonamido - pyrimidine. m.p. 237°C., yield 3.2 g.

Elemental analysis ($C_{12}H_{13}O_4N_5S$):

Calc.	C: 40.29%,	H: 3.38%,	N: 19.59%
Found	C: : 40.04%,	H: 3.62%,	N: 19.50%

3.2 g. of 2 - dimethylamino - 4 - *p* - nitro-benzenesulfonamido - pyrimidine thus obtained were dissolved in 100 c.c. of methanol, and was reduced catalytically with 0.2 g. of palladium-carbon. The reaction product was filtered. The residue resulting from distillation of methanol under reduced pressure was dissolved in water and then neutralized with 10% acqueous solution of sodium hydroxide to give white crystals. Recrystallization from methanol gave white prism crystals of the desired product. m.p. 145°C—147°C., yield 2.7 g.

Elemental analysis ($C_{12}H_{15}O_2N_5S$):

Calc.	C: 49.14%,	H: 5.16%,	N: 23.88%
Found	C: 49.47%,	H: 5.13%,	N: 23.43%

EXAMPLE 7.
6-dimethyl-4-sulfanilamido-pyrimidine

1.38 g. (0.01 mol) of 6 - dimethylamino-4 - amino - pyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzenesulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from methanol gave white needle crystals of 6 - dimethylamino - 4 - acetylsulfanilamido - pyrimidine. m.p. 296—297°C., yield 3.2 g.

Elemental analysis ($C_{14}H_{17}O_3N_5S$):

Calc.	C: 50.14%,	H: 5.11%,	N: 20.89%
Found	C: 49.84%,	H: 5.19%,	N: 20.57%

6 - dimethylamino - 4 - acetylsulfanilamido-pyrimidine thus obtained was subjected to the hydrolysis as in example 1. Recrystallization from dilute methanol gave the desired white scaly crystals. m.p. 276°C., yield 2.7 g.

From the results of elemental analysis, infra-red spectrum and mixed melting point examination, the present product was ascertained to be identical with that obtained in Example 5.

EXAMPLE 8.
2,6-bis-dimethylamino-4-sulfanilamido-pyrimidine

An admixture of 2 g. (0.01 mol) of 2.6 - bis-dimethylamino - 4 - chloro - pyrimidine and 4 g. (0.0206 mol) of sodium salt of sulfanilamide was added to 4 g. of acetamide at 60°C. with vigorous stirring. After reaction for 20 minutes at 75°C. the reaction product was added to 20 c.c. of water and neutralized with concentrated hydrochloric acid to give a deposit. The deposit was dissolved in 30 c.c. of a 10% aqueous solution of sodium hydroxide under heating, treated with activated carbon and then kept to stand in a cooled place, whereupon needle crystals of the sodium salt of 2.6 - bis - dimethylamino - 4 - sulfanilamido-pyrimidine deposited. Due to the influence of substitution of two dimethylamino radicals the present product is different from the usual sulfanilamides and dissolves with difficulty in the cold in caustic soda and caustic potash. Thus the product can be recrystallized in the form of sodium salt from the 10% aqueous solution. Said sodium salt, however, dissolves in water of pH 7.0. m.p. more than 300°C.

The sodium salt of 2.6 - bis - dimethylamino - 4 - sulfanilamido pyrimidine thus obtained was dissolved in water and neutralized with acetic acid to give crystals. Recrystallization from methanol gave white needle crystals of the desired product. m.p. 223—224°C., yield 2.4 g.

Elemental analysis ($C_{14}H_{20}O_2N_6S$):

Calc.	C: 49.99%,	H: 5.99%,	N: 24.99%
Found	C: 49.73%,	H: 5.98%,	N: 24.60%

EXAMPLE 9.
2.6-bis-dimethylamino-4-sulfanilamido-pyrimidine

1.81 g. (0.01 mol) of 2.6 - bis - dimethylamino - 4 - aminopyrimidine and 2.34 g. (0.01 mol) of *p* - acetamidobenzenesulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from methanol gave white needle crystals of 2.6 - bis-dimethylamino - 4 - acetylsulfanilamido-pyrimidine. m.p. 235°C., yield 3.5 g.

Elemental analysis ($C_{16}H_{22}O_3N_6S$):

Calc.	C: 50.78%,	H: 5.86%,	N: 22.21%
Found	C: 50.40%,	H: 5.72%,	N: 22.57%

3.5 g. of 2.6 - bis - dimethylamino - 4-acetylsulfanilamido - pyrimidine were dissolved in a mixed solution of 30 c.c. of 10% sodium hydroxide solution and 30 c.c. of methanol and caused to react at 70—80°C. for 3 hours on a water bath. The solution was kept to stand in cold place to deposit white needle crystals. Said crystals were recovered by filtration, dissolved in 30 c.c. of water and neutralized with acetic acid to deposit crystals. Recrystallization from methanol gave white needle crystals of the desired product. m.p. 223—224°C., yield 2.6 g.

From the results of elemental analysis, infrared spectrum and mixed melting point examination, the present product was ascertained to be identical with one obtained in example 7.

EXAMPLE 10.
2-dimethylamino-6-chloro-4-sulfanilamido-pyrimidine

1.72 g. (0.01 mol) of 2 - dimethylamino-6 - chloro - 4 - amino - pyrimidine and 2.2 g. (0.01 mol) of *p*-nitrobenzenesufonyl-chloride were dissolved in 2.2 c.c. of anhydrous pyridine and left to stand at room temperature for one night. The reaction mixture was poured into 100 c.c. of water. Recrystallization of the deposits formed from dilute methanol gave 2 - dimethylamino - 6 - chloro-4 - *p* - nitrobenzenesulfonamido - pyrimidine. m.p. 182—183°C., yield 3.4 g.

Elemental analysis ($C_{12}H_{12}O_4N_5SCl$):

Calc.	C: 40.29%,	H: 3.38%,	N: 19.59%
Found	C: 40.04%,	H: 3.62%,	N: 19.50%

3.4 g. of 2 - dimethylamino - 6 - chloro-4 - *p* - nitrobenzenesulfanamido - pyrimidine thus obtained were dissolved in a mixture of 100 c.c. of 95% ethanol and 10 c.c. of concentrated hydrochloric acid. 100 g. of iron powder was added to the solution under heating and stirring. After reaction for 14 hours under heating, the reaction product was filtered

while hot. The residue was washed several times with ethanol. From the mixture of the washed liquid and the mother liquid obtained previously, ethanol was distilled off under reduced pressure. The residue solidified. Recrystallization from dilute methanol gave white plate crystals of the desired product. m.p. 203—204°C., yield 2.9 g.

Elemental analysis ($C_{12}H_{14}O_2N_6SCl$):

Calc.	C: 43.97%,	H: 4.31%,	N: 21.33%
Found	C: 44.06%,	H: 4.55%,	N: 21.00%

EXAMPLE 11.
2-dimethylamino-6-chloro-4-sulfanilamido-pyrimidine

9.7 g. (0.05 mol) of dried sulfanilamide sodium salt and 8 g. (1.35 mol) of acetamide were heated to 160°C. Almost all of the sulfanilamide sodium salt dissolved. After cooling to 80—100°C., 6.4 g. (0.0183 mol) of the mono - trimethylammonium adduct of 2-dimethylamino - 4.6 - dichloro - pyrimidine were added under stirring, whereupon trimethylamine was evolved. For completion of the evolution, the mixture was heated for a short time. The residue resulting from distillation of acetamide at 180°C. under reduced pressure, completely dissolved on addition of 40 c.c. of water. When the solution was left to stand in ice room for a long time the raw material sulfanylamide deposited. After removal of the deposits by filtration, the mother liquid was adjusted to pH 6.0 with concentrated hydrochloric acid to give the desired crude product of m.p. 200°C. Recrystallization of the product from dilute methanol gave white plate crystals of the desired product. m.p. 203—204°C., yield 4.25 g.

From the results of elemental analysis, infrared spectrum and mixed melting point examination, the present product was ascertained to be identical with one obtained in example 9.

Elemental analysis ($C_{12}H_{14}O_2N_6SCl$):

Calc.	C: 43.97%,	H: 4.33%,	N: 21.33%
Found	C: 44.10%,	H: 4.18%,	N: 21.63%

EXAMPLE 12.
2-dimethylamino-6-chloro-4-sulfanilamido-pyrimidine

1.72 g. (0.01 mol) of 2 - dimethylamino - 6-chloro - 4 - aminopyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzenesulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from methanol gave 2 - dimethylamino - 6 - chloro - 4 - acetylsulfanilamidopyrimidine. m.p. 216°C., yield 3.5 g.

3.5 g. of 2 - dimethylamino - 6 - chloro-4 - acetylsulfanilamido - pyrimidine thus obtained were subjected to hydrolysis as in example 1. Recrystallization from dilute methanol gave the desired product. Yield 3.1 g.

From the results of elemental analysis, infrared spectrum and mixed melting point examination, the present product was ascertained to be identical with those obtained in examples 9 and 10.

EXAMPLE 13.
2-diethylamino-6-chloro-4-sulfanilamido-pyrimidine

2 g. (0.01 mol) of 2 - diethylamino - 6-chloro - 4 - amino - pyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzenesulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from methanol gave 2 - diethylamino-6 - chloro - 4 - acetylsulfanilamidopyrimidine. m.p. 194°C., yield 3.8 g.

Elemental analysis ($C_{16}H_{20}O_3N_6SCl$):

Calc.	C: 48.30%,	H: 5.07%,	N: 17.61%
Found	C: 48.40%,	H: 5.02%,	N: 18.05%

3.8 g. of 2 - diethylamino - 6 - chloro - 4-acetylsulfanilamido - pyrimidine thus obtained were subjected to hydrolysis by usual way. The hydrolysis can be easily carried out by caustic soda but it may be also performed even by 20% hydrochloric acid solution. Recrystallization from dilute methanol gave white plate crystals of the desired product. m.p. 164°C., yield 3.4 g.

Elemental analysis ($C_{14}H_{18}O_3N_5SCl$):

Calc.	C: 47.26%,	H: 5.10%,	N: 19.67%
Found	C: 47.60%,	H: 5.28%,	N: 19.68%

EXAMPLE 14.

2-dimethylamino-6-methoxy-4-sulfanilamido-pyrimidine

1.68 g. (0.01 mol) of 2 - dimethylamino-6 - methoxy 4 - amino - pyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzenesulfonylchloride were dissolved in 2.3 cc. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from methanol gave white column crystals of 2 - dimethylamino - 6 - methoxy-4 - acetylsulfanilamido - pyrimidine, m.p. 251°C., yield 3.5 g.

Elemental analysis ($C_{15}H_{19}O_4N_5S$):

Calc.	C: 49.31%,	H: 5.24%,	N: 19.19%
Found	C: 49.52%,	H: 5.48%,	N: 19.20%

3.5 g. of 2 - dimethylamino - 6 - methoxy-4 - acetylsulfanilamido - pyrimidine thus obtained were subjected to hydrolysis as in example 1. Recrystallization from dilute methanol gave white plate crystals of the desired product. m.p. 220°C., yield 3 g.

Elemental analysis ($C_{13}H_{17}O_3N_5S$):

Calc.	C: 48.29%,	H: 5.30%,	N: 21.66%
Found	C: 48.11%,	H: 5.20%,	N: 21.26%

The mixed melting point examination of the present product with the product obtained in example 1 shown clearly the depression of melting point, so that the present product was an isomer having different substituted position.

EXAMPLE 15.

2 - dimethylamino-6-ethoxy-4-sulfanilamido-pyrimidine

1.82 g. (0.01 mol) of 2 - dimethylamino-6 - ethoxy - 4 - aminopyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzenesulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from diluted methanol gave white needle crystals of 2 - dimethylamino - 6-ethoxy - 4 - acetylsulfanilamido - pyrimidine. m.p. 223—224°C., yield 3.6 g.

Elemental analysis ($C_{14}H_{21}O_4N_5S$):

Calc.	C: 50.65%,	H: 5.58%,	N: 18.46%
Found	C: 50.45%,	H: 5.70%,	N: 18.17%

3.6 g. of 2 - dimethylamino - 6 - ethoxy-4 - acetylsulfanilamido - pyrimidine thus obtained were subjected to hydrolysis in the usual way. Recrystallization from dilute methanol gave white plate crystals of the desired product. m.p. 186°C., yield 3.1 g.

Elemental analysis ($C_{14}H_{19}O_3N_5S$):

Calc.	C: 49.84%,	H: 5.68%,	N: 20.76%
Found	C: 49.62%,	H: 5.68%,	N: 20.90%

EXAMPLE 16.

2-dimethylamino-6-n-propoxy-4-sulfanilamido-pyrimidine

1.96 g. (0.01 mol) of 2 - dimethylamino-6 - n - propoxy - 4 - amino - pyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzenesulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procesure as in example 1. Recrystallization from dilute methanol gave light yellow plate crystals of 2 - dimethylamino - 6 - n-propoxy - 4 - acetylsulfanilamido - pyrimidine. m.p. 162°C., yield 3.5 g.

Elemental analysis ($C_{17}H_{23}O_4N_5S$):

Calc. C: 51.90%, H: 5.89%, N: 17.80%
Found C: 51.67%, H: 6.21%, N: 18.11%

3.5 g. of 2 - dimethylamino - 6 - n-propoxy - 4 - acetylsulfanilamido - pyrimidine thus obtained were subjected to hydrolysis by usual way. Recrystallization from dilute methanol gave white plate crystals of the desired product. m.p. 91°C., yield 3 g.

Elemental analysis ($C_{15}H_{21}O_3N_5S$):

Calc. C: 51.27%, H: 6.02%, N: 19.93%
Found C: 51.05%, H: 6.14%, N: 20.10%

EXAMPLE 17

2-dimethylamino-6-ethylthio-4-sulfanilamido-pyrimidine

1.89 g. (0.01 mol) of 2 - dimethylamino-6 - ethylthio - 4 - amino - pyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzene-sulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from dilute methanol gave 2-dimethylamino - 6 - ethylthio - 4 - acetylsulfanilamido - pyrimidine. m.p. 225—226°C., yield 3.6 g.

Elemental analysis ($C_{16}H_{21}O_3N_5S_2$):

Calc. C: 48.60%, H: 5.35%, N: 17.72%
Found C: 48.97%, H: 5.46%, N: 17.79%

3.6 g. of 2 - dimethylamino - 6 - ethylthio-4 - acetylsulfanilamido - pyrimidine thus obtained were subjected to hydrolysis by usual way. Recrystallization from dilute methanol gave white plate crystals of the desired product. m.p. 139°C., yield 3.1 g.

Elemental analysis ($C_{14}H_{19}O_2N_5S$):

Calc. C: 47.59%, H: 5.42%, N: 19.82%
Found C: 47.45%, H: 5.58%, N: 19.75%

EXAMPLE 18.

2 - dimethylamino - 6 - n - propylthio-4-sulfanilamido-pyrimidine

2.12 g. (0.01 mol) of 2 - dimethylamino-6 - n - propylthio - 4 - amino - pyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzene-sulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from dilute methanol gave white column crystals of 2 - dimethylamino - 6-n - propylthio - 4 - acetylsulfanylamido-pyrimidine. m.p. 205°C., yield 3.8 g.

Elemental analysis ($C_{17}H_{23}O_3N_5S_2$):

Calc. C: 49.87%, H: 5.66%, N: 17.11%
Found C: 50.06%, H: 5.73%, N: 16.96%

3.8 g. of 2 - dimethylamino - 6 - n-propylthio - 4 - acetylsulfanilamido-pyrimidine thus obtained were dissolved in 40 c.c. of 10% aqueous solution of sodium hydroxide and heated at 90—100°C. for 2 hours. On acidification with acetic acid crystals deposited. Recrystallization from dilute methanol gave the desired product. m.p. 167°C., yield 3.2 g.

Elemental analysis ($C_{15}H_{21}O_2N_5S_2$):

Calc. C: 49.04%, H: 5.76%, N: 19.07%
Found C: 49.42%, H: 5.97%, N: 18.86%

EXAMPLE 19
2-dimethylamino-6-i-propylthio-4-sulfanilamido-pyrimidine

2.12 g. (0.01 mol) of 2 - dimethylamino-6 - i - propylthio - 4 - amino - pyrimidine and 2.3 g. (0.01 mol) of *p*-acetamidobenzenesulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from dilute methanol gave 2-dimethylamino - 6 - i - propylthio - 4 - acetylsulfanilamido - pyrimidine. m.p. 182°C., yield 3.9 g.

Elemental analysis ($C_{17}H_{23}O_3N_5S_2$):

Calc. C: 49.87%, H: 5.66%, N: 17.11%
Found C: 49.95%, H: 5.51%, N: 17.33%

3.9 g. of 2 - dimethylamino - 6 - i - propylthio - 4 - acetylsulfanilamido - pyrimidine thus obtained were subjected to hydrolysis by usual way. Recrystallization from dilute methanol gave white plate crystals of the desired product. m.p. 171°C., yield 3.3 g.

Elemental analysis ($C_{16}H_{21}O_2N_5S_2$):

Calc. C: 49.04%, H: 5.76%, N: 19.07%
Found C: 49.58%, H: 5.98%, N: 19.05%

EXAMPLE 20.
2-methylthio-6-dimethylamino-4-sulfanilamido-pyrimidine

1.84 g. (0.01 mol) of 2 - methylthio - 6-dimethylamino - 4 - aminopyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzenesulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from methanol gave 2 - methylthio-6 - dimethylamino - 4 - acetylsulfanilamido-pyrimidine. Yield 3.1 g.

3.1 g. of 2 - methylthio - 6 - dimethylamino - 4 - acetylsulfanilamido - pyrimidine thus obtained were dissolved in a mixture of 40 c.c. of 10% aqueous solution of sodium hydroxide and 10 c.c. of methanol and subjected to reflux on a water bath at 80—90°C. for 4 hours. Neutralization with acetic acid after cooling gave a precipitate. Recrystallization from methanol gave light yellow fine needle crystals of the desired product. m.p. 242—243°C., yield 2.9 g.

Elemental analysis ($C_{13}H_{17}O_2N_5S_2$):

Calc. C: 46.01%, H: 5.05%, N: 20.64%
Found C: 46.22%, H: 5.40%, N: 20.62%

EXAMPLE 21.
2-pyrrolidino-6-chloro-4-sulfanilamido-pyrimidine

1.98 g. (0.01 mol) of 2 - pyrrolidino - 6-chloro - 4 - amino - pyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzenesulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from dilute methanol gave light yellow scaly crystals of 2 - pyrrolidino - 6 - chloro-4 - acetylsulfanilamido - pyrimidine. m.p. 241°C., yield 3.6 g.

3.6 g. of 2 - pyrrolidino - 6 - chloro - 4-acetylsulfanilamido - pyrimidine thus obtained were dissolved in a mixture of 40 c.c. of 10% aqueous solution of sodium hydroxide and 100 c.c. of methanol and heated on a water bath at 80—90°C. for 4 hours. On cooling, the sodium salt of 2 - pyrrolidino - 6 - chloro-4 - sulfanilamido - pyrimidine was deposited in a form of needle crystals. m.p. over 300°C. The crystals recovered by filtration were dissolved in 300 c.c. of water and adjusted to pH 6.0 with acetic acid to give 3.1 g. of free 2 - pyrrolidino - 6 - chloro - 4 - sulfanilamido - pyrimidine. Recrystallization from a mixed solvent of acetone and water gave white needle crystals of the desired product. m.p. 234°C., yield 2.8 g.

Elemental analysis ($C_{14}H_{16}O_2N_5SCl$):

Calc. C: 47.53%, H: 4.55%, N: 19.80%
Found C: 47.55%, H: 4.38%, N: 19.81%

EXAMPLE 22.
2-diallylamino - 6 - chloro - 4-sulfanilamido-pyrimidine

2.24 g. (0.01 mol) of 2 - diallylamino - 6-chloro - 4 - aminopyrimidine and 2.34 g. (0.01 mol) of *p*-acetamidobenzenesulfonylchloride were dissolved in 2.3 c.c. of anhydrous pyridine and subjected to the same reaction procedure as in example 1. Recrystallization from dilute alcohol gave white scaly crystals of 2 - diallylamino - 6 - chloro - 4 - acetylsulfanilamido-pyrimidine. m.p. 183—185°C., yield 3.8 g.

3.8 g. of 2 - diallylamino - 6 - chloro - 4-acetylsulfanilamido - pyrimidine thus obtained were subjected to hydrolysis with methanolic caustic soda. Recrystallization from methanol gave the desired crystalline product. m.p. 172—173°C., yield 3.3 g.

Elemental analysis ($C_{16}H_{18}O_2N_5SCl$):

Calc.	C: 50.59%,	H: 4.77%,	N: 18.44%
Found	C: 50.55%,	H: 4.56%,	N: 18.42%

EXAMPLE 23.
2-morpholino-6-chloro-4-sulfanilamido-pyrimidine.

2.15 g. (0.01 mol) of 2 - morpholino - 6-chloro - 4 - amino - pyrimidine and 2.34 g. (0.01 mol) of *p* - acetamidobenzenesulfonyl-chloride were dissolved in 2.3 c.c. of anhydrous pyridine, and subjected to the same reaction procedure as in example 1. Recrystallization from methanol gave white needle crystals of 2 - morpholino - 6 - chloro - 4 - acetyl-sulfanilamilo - pyrimidine. m.p. 274°C., yield 3.8 g.

Elemental analysis ($C_{16}H_{18}O_4N_5SCl$):

Calc.	C: 46.66%,	H: 4.40%,	N: 17.00%
Found	C: 46.62%,	H: 4.47%,	N: 17.21%

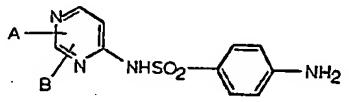
3.8 g. of 2 - morpholino - 6 - chloro - 4-acetylsulfanilamido - pyrimidine thus obtained were subjected to hydrolysis as in example 1. Recrystallization from dilute methanol gave white scaly crystals of the desired product. m.p. 271°C., yield 3.4 g.

Elemental analysis ($C_{14}H_{16}O_3N_5SCl$):

Calc.	C: 45.46%,	H: 4.36%,	N: 18.94%
Found	C: 45.43%,	H: 4.29%,	N: 19.03%

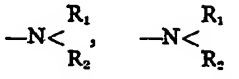
WHAT WE CLAIM IS:—

1. Novel 4 - sulfanilamido - pyrimidines having a substituted amino radical in the pyrimidine nucleus represented by the general formula:



wherein, A and B are respectively atoms or radicals combined at the 2 position and 6 position, one of them representing always

and the other hydrogen, halogen, alkoxy, alkylthio, or



being a radical in which R_1 and R_2 are aliphatic hydrocarbon residues or which forms a heterocyclic ring which may contain oxygen or sulfur atom in addition to R_1, R_2 and the adjacent nitrogen.

2. Salts of the novel 4 - sulfanilamido-pyrimidines claimed in claim 1.

3. 2 - alkoxy - 6 - dimethylamino - 4-sulfanilmido - pyrimidines.

4. 2 - dimethylamino - 4 - sulfanilamido-pyrimidine.

5. 6 - dimethylamino - 4 - sulfanilamido-pyrimidine.

6. 2,6 - bis - dimethylamino - 4 - sulfanil-amido - pyrimidine.

7. 2 - dimethylamino - 6 - chloro - 4-sulfanilamido - pyrimidine.

8. 2 - diethylamino - 6 - chloro - 4-

sulfanilamido - pyrimidine.

9. 2 - dimethylamino - 6 - alkoxy - 4- sulfanylamido - pyrimidines.

10. 2 - dimethylamino - 6 - alkylthio - 4- sulfanilamido - pyrimidines.

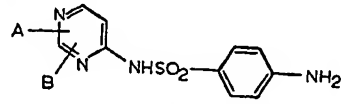
11. 2 - methylthio - 6 - dimethylamino - 4- sulfanilamido - pyrimidine.

12. 2 - pyrrolidino - 6 - chloro - 4- sulfanilamido - pyrimidine.

13. 2 - diallylamino - 6 - chloro - 4- sulfanilamido - pyrimidine.

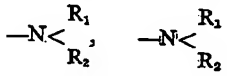
14. 2 - morpholino - 6 - chloro - 4- sulfanilamido - pyrimidine.

15. Process for manufacturing novel 4- sulfanilamido pyridines having a substituted amino radical in the pyrimidine nucleus represented by the general formula:

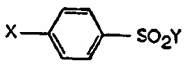


wherein A and B are respectively atoms or radicals combined at 2 position and 6 position, one of them representing always

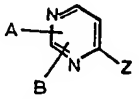
and the other hydrogen, halogen, alkoxy, alkylthio or



being a radical such that R_1 and R_2 are aliphatic hydrocarbon residue or that forms a heterocyclic ring containing or not containing oxygen or sulfur atom in addition to R_1, R_2 and the adjacent nitrogen atom, which comprises reacting compounds represented by the general formula



wherein X is an amino radical or a substituent capable of being converted into an amino radical by reduction or hydrolysis, for example, nitro, acylamino, alkoxycarbonylamino or azo radical and Y is NH_2, NHNa, or halogen, with compounds represented by the general formula:



wherein A and B are the same groups as above and Z is NH_2, NHNa, halogen or $N(CH_3)_3Cl$, but one of Y and Z is NH_2 or NHNa and the other is a halogen or $N(CH_3)_3Cl$, and if necessary converting the substituent X to an amino radical.

16. Process for manufacturing 2 - alkoxy- 6 - dimethylamino - 4 - sulfanilamido- pyrimidine which comprises condensing 2- alkoxy - 6 - dimethylamino - 4 - amino- pyrimidine with *p*-acetamido benzenesulfonyl- chloride in the presence of pyridine and hydrolysing the resulting product to convert the acetamido group into amine group.

17. Process for manufacturing 6 - dimethyl- amino - 4 - sulfanilamido - pyrimidine which comprises condensing 6 - dimethylamino - 4- chloropyrimidine with sulfanilamide in the presence of potassium carbonate and sodium chloride under heating.

18. Process for manufacturing 2 - dimethyl- amino - 4 - sulfanilamido - pyrimidine which comprises condensing 2 - dimethylamino - 4- amino - pyrimidine with *p* - nitro - benzene- sulfonyl chloride in the presence of pyridine (at room temperature) and reducing the resulting product to convert the nitro group into an amino group.

19. Process for manufacturing 6 - dimethyl- amino - 4 - sulfanilamido - pyrimidine which comprises condensing 6 - dimethylamino - 4- amino - pyrimidine with *p*-acetamidobenzene- sulfonylchloride in the presence of pyridine and hydrolysing the resulting product to convert the acetamido group into an amino group.

20. Process for manufacturing 2,6 - bis- dimethylamino - 4 - sulfanilamido - pyrimidine which comprises condensing a mixture of 2,6- bis - dimethylamino - 4 - chloro - pyrimidine and the sodium salt of sulfanilamide with acetamide under heating, neutralizing the reaction product with hydrochloric acid and treating with an alkali metal hydroxide under heating.

21. Process for manufacturing 2,6 - bis- dimethylamino - 4 - sulfanilamido - pyrimidine which comprises condensing 2,6 - bis- dimethylamino - 4 - aminopyrimidine with *p* - acetamidobenzenesulfonylchloride in the presence of pyridine and hydrolysing the resulting product to convert the acetamido group into an amino group.

22. Process for manufacturing 2 - dimethyl- amino - 6 - chloro - 4 - sulfanilamido- pyrimidine which comprises condensing 2- dimethylamino - 6 - chloro - 4 - amino- pyrimidine with *p* - nitro - benzenesulfonyl- chloride in the presence of pyridine and reducing the resulting product to convert the nitro group into an amino group.

23. Process for manufacturing the same product as in Claim 22 which comprises condensing the sodium salt of sulfanilamide with the mono-trimethylammonium salt of 2- dimethylamino-4,6 - dichloro - pyrimidine in the presence of acetamide under heating.

24. Process for manufacturing the same product as in Claim 22 which comprises condensing 2 dimethylamino - 6 - chloro - 4-amino - pyrimidine with *p*-acetamidobenzenesulfonylchloride in the presence of pyridine at room temperature and hydrolysing the resulting product to convert the acetamido group into an amino group.

25. Process for manufacturing 2 - diethylamino - 6 - chloro - 4 - sulfanilamidopyrimidine which comprises condensing 2-diethylamino - 6 - chloro - 4 - aminopyrimidine with *p*-acetaminobenzenesulfonylchloride in the presence of pyridine at room temperature and hydrolysing the resulting product to convert the acetamido group into an amino group.

26. Process for manufacturing 2 - dimethylamino - 6 - alkoxy - 4 - sulfanilamidopyrimidine which comprises condensing 2-dimethylamino - 6 - alkoxy - 4 - aminopyrimidine with *p*-acetamidobenzenesulfonylchloride in the presence of pyridine at room temperature and hydrolysing the resulting product to convert the acetamido group into an amino group.

27. Process for manufacturing 2 - dimethylamino - 6 - alkylthio - 4 - sulfanilamidopyrimidine which comprises condensing 2-dimethylamino - 6 - alkylthio - 4 - aminopyrimidine with *p*-acetamidobenzenesulfonylchloride in the presence of pyridine at room temperature and hydrolysing the resulting product to convert the acetamide group into an amino group.

28. Process for manufacturing 2 - methylthio - 6 - dimethylamino - 4 - sulfanilamidopyrimidine which comprises condensing 2-methylthio - 6 - dimethylamino - 4 - aminopyrimidine with *p*-acetamidobenzenesulfonylchloride in the presence of pyridine at room temperature and hydrolysing the resulting product to convert the acetamido group into an amino group.

29. Process for manufacturing 2 - pyrrolidino - 6 - chloro - 4 - sulfanylamidopyrimidine which comprises condensing 2-pyrrolidino - 6 - chloro - 4 - aminopyrimidine with *p*-acetamido-benzenesulfonylchloride in the presence of anhydrous pyridine at room temperature and hydrolysing the resulting product to convert the acetamido group into an amino group.

30. Process for manufacturing 2 - diallylamino - 6 - chloro - 4 - sulfanilamidopyrimidine which comprises condensing 2-alylamino - 6 - chloro - 4 - aminopyrimidine with *p* - acetamidobenzenesulfonylchloride in the presence of pyridine at room temperature and hydrolysing the resulting product to convert the acetamido group into an amino group.

31. Process for manufacturing 2 - morpholino - 6 - chloro - 4 - sulfanilamidopyrimidine which comprises condensing 2-morpholino - 6 - chloro - 4 - amino-pyrimidine with *p* - acetamidobenzenesulfonylchloride in the presence of pyridine at room temperature and hydrolysing the resulting product to convert the acetamido group into an amino group.

32. Process for manufacturing a salt of the 4 - sulfanilamido - pyrimidine derivatives as claimed in Claim 1 which comprises causing said derivatives to react with an alkali-metal carbonate, alkali-metal hydroxide or organic base.

33. Novel 4 - sulfanilamido - pyrimidines and their salts and process for the manufacture thereof substantially as set forth in any one of Examples 1 to 23 herein.

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